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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/00 — A1

(11) International Publication Number: **WO 98/18491**

(43) International Publication Date: 7 May 1998 (07.05.98)

(21) International Application Number: PCT/US97/19564

(22) International Filing Date: 28 October 1997 (28.10.97)

(30) Priority Data:
60/029,403 28 October 1996 (28.10.96) US

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(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHODS AND COMPOSITIONS FOR DIETARY SUPPLEMENTATION

(57) Abstract

The present invention provides a composition comprising thymic–derived factors and enzymatic co–factors, wherein the thymic–derived factors can be thymus extract, thymus enzymatic polypeptide factors, thymosin, thymopoietin and thymic humoral factor and the enzymatic co–factors can be vitamins A, C, D, E, B–1, B–2, B–6, B–12, minerals. The composition can also comprise amino acids which can be arginine, cysteine, histidine, ornithine, isoleucine, leucine, threonine, tyrosine, valine, phenylalanine and methionine. The composition of this invention can further comprise glandular factors which can be raw spleen, raw lymph, raw bone marrow and raw pituitary. Also provided are methods of increasing serum levels of thymosin alpha 1 in a subject; of enhancing the immune system of a subject by increasing serum levels of thymosin alpha 1 in the subject; of treating an autoimmune disease such as systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis in a subject; of treating a viral infection caused by a virus such as Hepatitis A virus, hepatitis B virus, herpes virus, hepatitis C virus and human immunodeficiency virus in a subject; and of enhancing athletic performance in a subject by increasing hematocrit and reducing recovery time in the subject, wherein all of these methods comprise administering to the subject the compositions of the present invention.

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METHODS AND COMPOSITIONS FOR DIETARY SUPPLEMENTATION

Technical Field

The present invention comprises methods for supplementing the diet, including improving the functioning of the immune system. The present invention also comprises compositions that supplement the diet by providing cofactors and other dietary elements including vitamins and minerals.

Background of the Invention

Dietary supplementation may provide an additional methodology for, or alternative route to, traditional medical techniques for enhancing the overall health of humans and particularly for stimulating the immune system. Diet has been shown to have subtle and long-term effects on human and animal health and well-being. For example, high fat diets have been implicated in several kinds of cancers and heart disease.

The body constantly undergoes complex chemical conversions that require factors, cofactors and coenzymes to aid the enzymes involved in the conversions. One of the sources for such factors, cofactors and coenzymes is the food that is ingested. There is no assurance that a random diet will provide the necessary factors and cofactors. In fact, many diets are inadequate to meet the nutritional needs of the body, much less provide factors that enhance the workings of the body. Even so-called good diets may not provide enough of the necessary kinds of factors or co-factors for optimum health for a normal, healthy human or animal.

For humans and animals experiencing ill health, due to infectious agents, immune dysfunction, stress, cancer, poor care or for other reasons, the requirements for nutritional supplementation are even greater than for healthy bodies. An ill body is a body that is not functioning normally, and thus additional types or amounts of factors or cofactors are more necessary than if the body was healthy. Additionally, the ill body

may need greater amounts of certain factors or co-factors to repair and rebuild dysfunctional cells or organs.

Many illnesses cause an increase in the mitotic rate of cells and thus, the cells require more cellular enzymatic reactions. The increased rate of mitosis requires more starting materials such as proteins for structural and enzymatic functions and fats for energy conversion. Increased enzymatic reactions cause an increase in the turnover of factors and co-factors involved in the enzymatic reactions. Persons with such illnesses would need dietary supplementation to meet the increased demand for factors and co-factors.

One of the systems of the human body that is essential for maintaining good health is the immune system. The immune system is a highly complex system of cells and tissues that requires the cooperation of a large number of different cell types. By circulating its component cells and substances, the immune system maintains an early warning system against both exogenous infectious agents and from endogenous cellular changes, such as cancer. The immune system can provide a variety of reactions and can magnify or restrain the response. The systems of the body that make up the immune system network are variously categorized as belonging to the hematopoietic system, the reticuloendothelial or phagocytic system and the lymphoid system.

The hematopoietic system is located in the bone marrow and is responsible for supplying the various precursor and accessory cells of the immune system. The reticuloendothelial system is made up of the phagocytic cells that are responsible for destroying or neutralizing foreign material that may enter the body. The lymphoid system is made up of lymphocytes, and is responsible for the overall regulation of the immune system and for the production of antibodies.

The tissues of the lymphoid system are generally classified as the central tissues and the peripheral tissues. Two central lymphoid tissues of mammals are bone marrow

and thymus. In addition, fowl have a third central lymphoid organ, the bursa of Fabricius, which is critical to the development of the immunoglobulin-producing cells, the B-cells. It is thought that the mammals have a bursal equivalent associated with the intestinal tract. Lymph nodes, spleen, tonsils, intestinal lymphoid tissue (Peyer's patches) and other collections of lymphocytes constitute the peripheral lymphoid tissues.

In mammals, the bone marrow, if considered as a single tissue, is the largest tissue of the body. In the average human adult, the total weight of the bone marrow is about 3 kg. Marrow fills the central core of nearly all bones. Bone marrow has three types of tissue; vascular tissue, adipose tissue and the tissue directed to hematopoiesis or blood cell formation. The vascular tissue is the circulatory system that supplies nutrients and removes wastes from the actively growing cells. The hematopoietic tissue is responsible for the formation of cells including erythrocytes, platelets, granulocytes, monocytes and lymphocyte precursors. Adipose tissue consists of fat cells which contribute little to the function of the bone marrow.

The other central lymphoid tissue is the thymus. In humans, this bilobed organ is situated in the anterior thoracic cage over the heart. In other species, the thymus may be distributed along the neck and thorax in several lobules.

Embryologically, the thymus emerges from the third and fourth branchial pouches. The human thymus is a fully developed organ at birth and weighs 15 to 20 grams. By puberty it weighs 40 grams, after which it atrophies or involutes becoming less significant structurally and functionally. Atrophy of the thymus with age is a characteristic of all species and is associated with aging and the cessation of growth. The incidence of age related diseases increases as the thymus shrinks and thymus-dependent immunity decreases. This age-associated involution of the thymus, resulting in a decrease in thymic weight, is accompanied by changes in the thymic structure and a general decline in thymic function. Transient involution of the thymus may also occur as a consequence of stress or infection.

Thymic involution may be controlled hormonally. Castration slows involution while injection of corticosteroid hormones accelerates involution. Numerous studies have demonstrated that the thymic involution associated with increasing age parallels a reduction of T-lymphocyte-mediated immunity and increased incidence of diseases associated with aging. Many diseases and treatments can accelerate involution of the thymus. Virtually no diseases or treatments are known to enhance growth of the thymus or reverse involution.

Anatomically, the thymus is a pouch of epithelial cells filled with lymphocytes, that is nourished and drained by the vascular and lymphatic systems and is innervated by the autonomic nerves. The epithelial cells and other structural cells divide the thymus into a complex assembly of continuous lobes, each of which is heavily laden with lymphocytes. The epithelial cells produce hormones and regulate some of the activities of the lymphocytes. The lymphocyte population is greatest in the cortex or outer portion of each lobule. The inner section, the medulla, has more epithelial cells and fewer lymphocytes but the lymphocytes are more mature.

Lymphocytes can generally be classified as either T-lymphocytes or as B-lymphocytes. B-lymphocytes are responsible for the production of antibodies (immunoglobulins) in response to a challenge by a particular antigen. These antibodies provide the humoral immunity for the body. The humoral immunity protects the body against bacteria, some viruses and microbial toxins. There are primary humoral responses to antigens and secondary responses to antigens. As in all immune responses, if the response is regulated, immunity is provided, but if unregulated, autoimmunity or death can result. For example, vaccination usually provides a long-lasting cellular memory that protects the body against infection by the agent of the vaccine. In contrast, some animals respond to a subsequent exposure to the immunostimulating agent by anaphylactic shock or death.

T-lymphocytes are responsible for the general regulation of the immune system and are also the principal mediators in cell-mediated immune responses. Cell-mediated immunity is important in protection against antigens such as fungi, viruses, rickettsiae, tuberculosis bacteria, transplanted tissues and tumor cells. T-cells also influence the proliferation of bone marrow cells and are probably involved in the growth and differentiation of other organs as well.

All lymphocytes are ultimately derived from stem cells in bone marrow. These lymphocyte precursors are dispersed into the blood where they course through many organs. However, critical events take place in the thymus and bursa of Fabricius (or its mammalian equivalent) that imprint the lymphocytes with special functions and that regulate the development into either T or B-lymphocytes.

The thymus is an important organ in the development and maintenance of the immune system. The thymus gland produces many hormones essential to the development and maturation of T lymphocytes. Thymic hormones that have been isolated and used to treat immune disorders include thymin, thymosin, and facteur thymique serique. Such factors derived from the thymus gland are being used to restore cell-mediated immunity in patients with acquired and congenital immune disorders and autoimmune diseases.

Life-span studies of lymphocytes of most mammalian species divide lymphocytes into two fractions; those with a short span (mostly large lymphocytes) of 5 to 7 days and the small lymphocytes with a life span measured in months or even years. The former are usually B-lymphocytes and the latter are usually T-lymphocytes.

T-lymphocytes are formed in the thymus from lymphoblasts that left the bone marrow. This maturation is expressed morphologically as a reduction in cell size to about 7 μm in diameter. The thymic cortex is rich in lymphocytes of all sizes. These thymocytes are not morphologically distinguishable from lymphocytes in other tissues,

but they are immature and antigenically identifiable by the presence of several cell surface antigens including the ø, or T antigen, a distinctive surface marker antigen that separates the T-lymphocyte from the B-lymphocyte.

Enumeration of lymphocytes indicate that 65% to 85% of all lymphocytes in the blood are of the T type. Lymphocytes of the thoracic duct fluid are nearly 90% to 95% of the T variety and those in the Peyer's patches or of the gut are 50% to 65% T-lymphocytes. The T-lymphocyte population of lymph nodes, particularly in the deep cortical region, is high, but is low in the tonsil and the appendix.

T-lymphocytes are actually divided into several subsets and the role that they play in the immune system is complex. The T-lymphocyte is responsible for the phenomenon known as the cell-mediated immune response. In a cell-mediated immune response, the T lymphocytes that recognize a cell-bound antigen begin producing and secreting a wide variety of proteins that affect the activity of other types of cells in the immune system. These proteins include lymphokines that attract, activate and hold phagocytes at the site of the antigen and interferons that provide protection against virus infection.

When the T-lymphocyte contacts a recognizable antigen in the appropriate context, it passes through a phase of growth and cell division known as lymphocyte transformation to produce a large population of its own kind. The antigen must first be "processed" by macrophages and then presented to T-lymphocytes.

The T-lymphocyte is also an important regulator of B-lymphocyte function. The antigen-exposed T-lymphocyte may have either of two direct and opposite effects on B-lymphocytes depending on the subclass of T-lymphocyte. The major subclasses are the helper cell and the suppressor cell. Helper T-lymphocytes are necessary for a complete B cell response to T-lymphocyte-dependent antigens. T-lymphocyte dependent

antigens tend to be the more complex antigens such as bacterial proteins, virus proteins and other large complex proteins in general.

Unlike helper T-lymphocytes, suppressor T-lymphocytes block the development of effector B and T lymphocytes. Specific suppressor T-lymphocytes have now been demonstrated to play a large role in tolerance to many proteins, both in antibody and cell-mediated immune responses. In addition, genetic unresponsiveness to some antigens is due to the greater stimulation of suppressor T-lymphocytes than of helper T-lymphocytes by these antigens.

In the normal, healthy animal, the thymus is normally active only during the early years of life. During these early years of thymic activity, the thymus supplies the animal with the T-lymphocytes which will serve the animal for the rest of its life. In certain diseases, such as rheumatoid arthritis, the thymus may regain some activity during adult life. This demonstrates that the adult thymus retains capacity to function and that involution is not necessarily permanent. At least partial function might be restored if the appropriate agents were available or if some of the thymus functions or factors could be replaced via the diet.

Acquired T-lymphocyte deficiency diseases of adults are characterized by a depletion of circulating T-lymphocytes. The symptoms expressed in these diseases include an inability to mount a cell-mediated immune response in response to an antigen challenge. An example of an acquired T-lymphocyte deficiency disease is acquired immune deficiency syndrome or AIDS.

AIDS is a disease caused by a virus that has had a variety of names including the human T-lymphocyte lymphotropic virus (LAV or HTLV-III) and human immunodeficiency virus. One proposal of how the virus causes disease is that the virus, which mutates readily, specifically attacks T-4 helper lymphocytes, a subgroup of T-lymphocytes that plays a major role in defending the body against infectious diseases.

Depletion of this subset of lymphocytes is manifested by an increased incidence of opportunistic infections caused by pathogens such as *Pneumocystis carinii*, as well as certain cancers. More specifically, the virus enters the T-lymphocyte and incorporates viral encoded DNA into the DNA of the host T-lymphocyte. As long as the infected T-lymphocyte remains inactivated, the virus will quietly remain in the DNA of the host cell. This will not kill the cell but may impair its function. When the infected T-lymphocytes are activated by stimuli such as a specific antigen, the viral DNA in the host DNA is expressed and produces new viral particles. The host T-lymphocyte is then killed and lysed, releasing new viral particles that can invade and kill other T-lymphocytes. The loss of T-4 lymphocytes is profound and occurs even faster than can be accounted for by direct viral killing of the cells. This has led some investigators to postulate that the infection somehow shuts off the production of T-4 lymphocytes. In any case, the thymus in the normal adult is no longer functioning and the killed T-lymphocytes cannot be replaced, leaving the patient vulnerable to subsequent infections. Especially striking are recent studies of the thymuses of deceased AIDS patients ranging in age from 10 months to 42 years. AIDS victims have profound thymic involution that is much more extensive than in age-matched patients who died of other causes.

The cure of a person with AIDS will probably require one agent to eliminate the virus and other agents to cause the body to replace T cells that have been killed by the virus. The first step is to eliminate the AIDS virus from the patient. This will have to be supported by other therapies to induce restoration of immune function. Studies to date with macrophage activating agents, interferon inducers and lymphokines have been disappointing, possibly because their targets, T-lymphocytes, do not exist in sufficient numbers. Interleukin 2 restores the function of one subset of non T-cells (natural killer cells) but has no effect on a host of other serious defects. More drastic measures can be performed. One potential method of restoring the immune system is by transplanting bone marrow from healthy donors. However, this is a dangerous procedure. It may produce lethal graft versus host disease unless the patient's donor is an identical twin.

Infection by other viruses is also effected when the immune system is not functioning at its peak. Because T-cells' cellular immunity is involved in protection against viruses, stimulation of T-cell like activity may cause protection or cessation of chronic viral infections such as those caused by the hepatitis viruses, including Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D or other such chronic disease-causing viruses. Though the above-listed hepatitis viruses are very different morphologically and are unrelated taxonomically, an enhanced immune response may provide protection from infection by any or all of them. This kind of general protection by the immune system cannot be provided by traditional medical techniques such as vaccination.

Autoimmune Diseases

Autoimmune diseases are characterized by the development of an immune reaction to self components. Normally, tissues of the body are protected from attack by the immune system. In autoimmune diseases, there is a breakdown of the self-protection mechanisms and an immune response directed to various components of the body ensues. Autoimmune diseases are for the most part chronic and require life long therapy. The number of recognized autoimmune diseases is large and consists of a continuum ranging from diseases affecting a single organ system to those affecting several organ systems. With increased understanding of the molecular basis of disease processes, many more diseases will likely be found to have an autoimmune component. Specific examples of autoimmune diseases are presented below.

Spectrum of Autoimmune Diseases

Organ Specific	Hashimoto's thyroiditis
	Graves' disease
	Addison's disease
	Juvenile diabetes (Type I)
	Myasthenia gravis
	Pemphigus vulgaris

	Sympathetic ophthalmia
	Multiple sclerosis
	Autoimmune hemolytic anemia
	Active chronic hepatitis
	Rheumatoid arthritis
Non-organ specific	Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an inflammatory, multi-system disease characterized clinically as a relapsing disease of acute or insidious onset that may involve any organ in the body. Clinically, symptoms are due to disease affecting the skin, kidneys, serosal membranes, joints and heart. Anatomically, all sites have in common vascular lesions with fibrinoid deposits and immunologically, the disease involves antibodies of autoimmune origin, especially antinuclear antibodies (ANA). The ANA are directed against both DNA and RNA. Autoantibody development appears to be multifactorial in origin, involving genetic, hormonal, immunologic and environmental factors.

The morphologic changes seen in organs result from the formation of circulating immune complexes and their deposition in a variety of tissues. Although many organs can be affected, some are affected more than others. Lesions of joints, the kidneys, heart, and serous membranes are responsible for most of the clinical signs. The course of SLE is extremely variable and unpredictable. An acute onset with progressive downhill course to death within months can occur. The usual course however, is characterized by flare-ups and remissions spanning a period of years or even decades. It usually arises in the second or third decades of life, but may become manifest at any age.

Acute attacks are usually treated by adrenocortical steroids or immunosuppressive drugs. These drugs often control the acute manifestations. With cessation of therapy, the disease usually reexacerbates. The prognosis has improved in

the recent past; approximately 70 to 80% of patients are alive 5 years after the onset of illness and 60% at 10 years. Lifelong therapy is required to control the disease.

At one time, SLE was considered to be a fairly rare disease. Better methods of diagnosis and increased awareness that it may be mild and insidious have made it evident that its prevalence may be as high as 1 case per 10,000 population. There is a strong female preponderance - about 10 to 1.

Rheumatoid arthritis is a systemic, chronic, inflammatory disease that affects principally the joints and sometimes many other organs and tissues throughout the body. The disease is characterized by a nonsuppurative proliferative synovitis, which in time leads to the destruction of articular cartilage and progressive disabling arthritis. The disease is caused by persistent and self-perpetuating inflammation resulting from immunologic processes taking place in the joints. As is the case with most autoimmune diseases, the trigger that initiates the immune reaction remains unidentified. Both humoral and cell mediated immune responses are involved in the pathogenesis of rheumatoid arthritis. The majority of patients have elevated levels of serum immunoglobulins and most patients have an antibody called rheumatoid factor (RF) directed against a component of another antibody class.

The key event in the pathogenesis of the arthritis is the formation of antibodies directed against other self antibodies. Why these antibodies are formed is unknown at present. It has been suggested that the process is initiated by the formation of antibodies or immunoglobulins against an unknown antigen, possibly an infectious agent. When the antibodies combine with the antigen, conformational changes occur in a portion of the antibody molecule, creating new antigenic determinants. The appearance of new determinants invokes an antibody response against the antibody molecule and results in the formation of anti-immunoglobulin antibodies or rheumatoid factor. T cells may also be involved in the pathogenesis of rheumatoid arthritis. A large number of T cells are found in the synovial membrane, outnumbering B cells and plasma cells. Additionally,

procedures to decrease the population of T cells (such as draining the thoracic duct), result in remission of symptoms.

The most destructive effects of rheumatoid arthritis are seen in the joints. Classically, it produces symmetric arthritis, which principally affects the small joints of the hands and feet, ankles, knees, wrists, elbows, shoulders, temporo-mandibular joints and sometimes the joints of the vertebral column. The clinical course is highly variable. After approximately 10 years, the disease in about 50% of the patients becomes stabilized or may even regress. Most of the remainder pursue a chronic, remitting, relapsing course. After 10 to 15 years, approximately 10% of patients become permanently and severely crippled.

The disease usually has its onset in young adults but may begin at any age and is 3 to 5 times more common in women than in men. Rheumatoid arthritis is a very common disease and is variously reported (depending on diagnostic criteria) to affect 0.5 to 3.8% of women and 0.1 to 1.3% of men in the United States.

Multiple sclerosis is another disease that is thought to be caused by autoimmune mechanisms. The cause of multiple sclerosis is unknown but seems to be multifactorial. Susceptibility or resistance may be genetically determined; something in the environment interacts with the human host at the proper age to cause biochemical and structural lesions in the central nervous system. The systemic immune response and the response of the central nervous system become involved. Although the cause and pathogenesis of multiple sclerosis are unknown, it is widely believed that immune abnormalities are somehow related to the disease. Three possible mechanisms have been postulated: infection, autoimmunity, and a combination of the two. Suppression or modulation of the immune responses may be the key.

The graphic distribution of multiple sclerosis indicate that the disease is acquired from an environmental factor. Approximately 200 studies of the geographic distribution

of multiple sclerosis have been conducted and have identified regions of high prevalence (30 to 80 cases per 100,000 population) in northern Europe between 65 and 45 degrees north latitude and in the northern United States and southern Canada, as well as in southern Australia and New Zealand. In contrast, regions of low risk, including most of Asia and Africa, have a prevalence of 5 or fewer cases per 100,000.

Myasthenia gravis is an autoimmune disorder caused by antibodies directed against the acetylcholine receptor of skeletal muscle. Present information indicates at least three mechanisms whereby acetylcholine receptor antibody may interfere with neuromuscular transmission and thus induce myasthenia gravis. Acetylcholine receptor antibody may interfere (directly or indirectly) with acetylcholine receptor function. In both experimental allergic myasthenia gravis and human myasthenia gravis, the extent of acetylcholine receptor loss parallels the clinical severity of the disease, suggesting that acetylcholine receptor antibody-induced acceleration of acetylcholine receptor degradation is important in the development of myasthenia gravis. Complement-mediated destruction of the postsynaptic region is the third possible cause. Other disorders, especially those presumed to be autoimmune in origin, can occur in association with myasthenia gravis. Thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, and pernicious anemia all occur more commonly with myasthenia gravis than would be expected by chance. The prevalence of myasthenia gravis in the United States is one per 20,000.

The foundation of therapy of autoimmune diseases is treatment with immunosuppressive agents. The basis for this therapy is attenuation of the self-directed immune response, with the primary aim being to control symptoms of the particular disease. The drugs utilized to achieve this aim are far from satisfactory, in that adverse side effects are numerous and control of the disease is often difficult to achieve. The problem is compounded by the chronicity of the disease, with effective therapy becoming more difficult with time. An indication of the severity of particular diseases is seen in the willingness to accept greater risks associated with therapy as the disease

progresses. Currently available therapy is distinctly non-selective in nature, having broad effects on both the humoral and cell mediated arms of the immune system. This lack of specificity can limit the effectiveness of certain therapeutic regimens. The main groups of chemical immunosuppressives are alkylating agents, antimetabolites, corticosteroids, and antibiotics, each of which will be discussed briefly.

The corticosteroids, also called adrenocorticosteroids, are fat-like compounds produced by the outer layer or cortex, of the adrenal gland. The adrenal cortex is an organ of homeostasis influencing the function of most systems in the body. It is responsible for adaptation of the body to a changing environment. Therapeutic use of the corticosteroids for autoimmune disease is based on their two primary effects on the immune system; anti-inflammatory action and destruction of susceptible lymphocytes. They also effect a redistribution of lymphocytes from peripheral blood back to the bone marrow. The use of corticosteroids is not without adverse side effects however, particularly during the course of life-long treatment which is required for many of the autoimmune diseases. Major side effects of steroids are:

1. Cushing syndrome
2. Muscle atrophy
3. Osteoporosis
4. Steroid induced diabetes
5. Atrophy of the adrenal glands
6. Interference with growth
7. Susceptibility to infections
8. Aseptic bone necrosis
9. Cataract development
10. Gastric ulcer
11. Steroid psychosis
12. Skin alterations
13. Nervous state accompanied by insomnia

Attempts to minimize side effects incorporate alternate day or less frequent dosage regimens.

An immunosuppressive agent is the antibiotic cyclosporin A. The antibiotic has greatest activity against T cells and does not seem to have much direct effect on B cells. The drug is being evaluated for the treatment of autoimmune diseases, for which it shows some promise. Side effects include hair growth, mild water retention and renal toxicity. In older patients, nervous system disorders symptoms have been observed.

Other drugs are used alone or in combination with those listed above and include gold salts and antimalarials, such as chloroquine. Another class of drugs, the nonsteroidal anti-inflammatory drugs are used extensively in arthritis. These drugs provide analgesia at low doses and are anti-inflammatory after repeated administration of high doses. Nonsteroidal anti-inflammatory drugs all act rapidly and their clinical effects decline promptly after cessation of therapy. They do not prevent the progression of rheumatoid arthritis and do not induce remissions. Immunostimulants, such as levamisol, have also been used in many autoimmune diseases but side effects have generally limited their use.

Summary of the Present Invention

The present invention includes compositions comprising thymic formulations and cofactors such as vitamins and minerals to supplement the diet. The present invention also comprises methods for supplementing the diet to provide cofactors and factors to improve or optimize the health of the human or animal. It is understood that the various components of the compositions of the present invention as described herein, such as thymic factors, thymic-derived factors, cofactors, enzymatic cofactors, glandular factors, vitamins, minerals, amino acids, etc., are those components which are effective in increasing the activity of the compositions of this invention (e.g., enhance an immune response or boost the immune system). In particular, the compositions include improved unitary delivery of the active factors that unexpectedly result in superior taste,

absorption and gastric transport when compared to prior multiple dose formulations. The unitary delivery formulation provides increased amounts of key ingredients and includes novel ingredients, thus enhancing the dietary supplementation and its attendant health benefits.

Such dietary supplementation is known to enhance the immune response of humans and to provide better overall health. For humans and animals in good health, the compositions and methods of the present invention aid in the maintenance of good health. For humans and animals with infectious agents such as viruses or bacteria, or for chronic immune dysfunction such as rheumatoid arthritis or systemic lupus erythematosus, the compositions and methods of the present invention provide enhanced dietary supplementation that allows for appropriate and enhanced immune responses and better nutrition to aid in the healing process.

The diet of humans and animals with immune dysfunction can be supplemented with the compositions of the present invention. Methods of diet supplementation can be used by humans and animals in good health for maintenance of good health. Methods of diet supplementation can be used by humans and animals with immune dysfunction or autoimmune diseases such as allergic reactions, systemic lupus erythematosus, multiple sclerosis, viral infections caused by Hepatitis B virus, Hepatitis C virus and human immunodeficiency viruses; animal immunodeficiency viruses and rheumatoid arthritis. Persons with other states of ill health such as psoriasis, squamous cell cancers and atopic dermatitis are also contemplated by the methods of the present invention for the supplementation of their diets.

Accordingly, it is an object of the present invention to provide a composition and method to supplement the diet of healthy humans and animals.

It is yet another object of the present invention to provide a composition and method for supplementing the diet of humans and animals with infectious diseases such as viral infections.

It is another object of the present invention to provide dietary supplementation for humans and animals with diseases mediated by autoimmune responses.

It is yet another object of the present invention to provide dietary supplementation for humans and animals with diseases mediated by a deficiency in their immune response.

It is yet another object of the present invention to provide dietary supplementation for persons infected with Hepatitis B virus.

It is yet another object of the present invention to provide dietary supplementation for persons infected with Hepatitis A virus.

It is yet another object of the present invention to provide dietary supplementation for persons infected with Hepatitis C virus.

It is yet another object of the present invention to provide dietary supplementation for persons infected with Hepatitis D virus.

It is yet another object of the present invention to provide dietary supplementation for humans and animals infected with immunodeficiency viruses.

It is yet another object of the present invention to provide dietary supplementation for humans and animals infected with a viral infection caused by a herpes virus.

It is another object of the present invention to provide a unitary formulation composition comprising thymic-derived factors and enzymatic cofactors such as vitamins and minerals.

Another object of the present invention is to provide a unitary formulation composition for dietary supplementation that is quickly absorbed by the body.

Another object of the present invention is to provide an all-in-one composition for dietary supplementation including glandular factors.

It is yet another object of the present invention to provide dietary supplementation for humans with psoriasis.

The present invention further provides a composition comprising thymic-derived factors and enzymatic co-factors, wherein the thymic-derived factors can be thymus extract, thymus enzymatic polypeptide factors, thymosin, thymopoietin and thymic humoral factor and the enzymatic co-factors can be vitamins A, D, C, E, B-1, B-2, B-6 and B-12 and minerals.

The composition of the present invention can further comprise glandular factors which can be raw spleen, raw lymph, raw bone marrow and raw pituitary and can be from a bovine source.

The composition of the present invention can also comprise amino acids such as arginine, cysteine, histidine, ornithine, isoleucine, leucine, threonine, tyrosine, valine, phenylalanine and methionine.

It is also contemplated that the present invention provides a composition consisting essentially of thymus enzymatic polypeptide fractions, thymus extract, raw spleen, raw lymph, raw bone marrow, raw pituitary, vitamins A, D, C, E, B-1, B-2, B-6

and B-12, folic acid, niacinamide, biotin, pantothenic acid, calcium, iodine, magnesium, copper, zinc, selenium, potassium, manganese, chromium, boron, hesperidin, inositol, citrus bioflavinoid, choline, betaine HCl, octacosanol, para amino benzoic acid, rutin, trypsin, bromelain, papain, Echinacea angustifolia extract, Iris versicolor extract, Hydrastis canadensis extract, L-lysine, L-arginine, L-cysteine, L-histidine, L-ornithine, L-isoleucine, L-leucine, L-threonine, L-valine, L-phenylalanine and L-methionine. In this composition, the thymus enzymatic polypeptide factors can be thymosin, thymopoietin and thymic humoral factor.

The present invention also provides a method of increasing serum levels of thymosin alpha 1 in a subject comprising administering to the subject the composition of the present invention.

A method is also provided for enhancing the immune system of a subject by increasing serum levels of thymosin alpha 1 in the subject comprising administering to the subject the composition of the present invention.

Further provided are methods of treating an autoimmune disease in a subject by increasing serum levels of thymosin alpha 1 and of treating an autoimmune disease in a subject, wherein the autoimmune disease can be systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis, comprising administering to the subject the composition of the present invention.

In addition, the present invention provides a method of treating a viral infection in a subject, which can be caused by a virus such as Hepatitis A virus, hepatitis B virus, herpes virus, hepatitis C virus and human immunodeficiency virus, comprising administering to the subject the composition of the present invention.

Furthermore, the present invention provides a method of enhancing athletic performance in a subject by increasing hematocrit and reducing recovery time in the subject comprising administering to the subject the composition of the present invention.

These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and the appended claims.

Detailed Description of the Preferred Embodiment

The present invention comprises methods and compositions for dietary supplementation for humans and animals with infectious diseases or immune dysfunction to enhance their immune functions in order to treat the disease or dysfunction. The present invention also comprises methods and compositions for dietary supplementation for healthy humans and animals to enhance their immune functions in order to maintain a healthy status.

The present invention also provides methods for enhancing athletic performance in a subject, comprising administering the composition of the present invention to the subject. In particular, the administration of the composition of the present invention to a subject (e.g., two doses three times a day for up to 60 days) results in an increase in total red blood cells in the subject, as demonstrated by increased hematocrit, thereby providing increased oxygen transport in the subject. In addition, administration of the compositions of the present invention to a subject results in a more rapid flushing of lactic acid from the muscles, providing a shorter recovery time after athletic activity. The increase in red blood cells and shorter recovery time allow for enhancement of the subject's athletic performance.

The compositions of the present invention comprise a formulation that comprises a quick absorption of the components. These novel compositions provide for the

unitary delivery of thymus and other glandular factors in association with vitamin and mineral compounds that are rapidly absorbed by the body.

Prior to the present invention, dietary supplementation involved multiple formulations in separate delivery vehicles that had to be taken in coordinated doses. The compositions of the present invention provide components in combinations that are different from previously known compositions, in a delivery system for faster absorption by the body.

The novel and improved compositions of the present invention are used for methods of dietary supplementation for enhancing the immune response of humans. A preferred composition includes the following elements. The measurements shown provide approximately the relative amounts of each element in a preferred composition.

Component	Relative Amount
Vitamin E (d-alpha tocopherol succinate)	66.6 IU
Vitamin C (Ascorbic Acid, buffered and esterified)	83.33 mg
Vitamin B-1 (Thiamine Mononitrate)	10 mg
Copper (Proteinate)	100 mcg
Zinc (Proteinate)	5 mg
Selenium (Proteinate)	18.33 mcg
L-Lysine	83.33 mg
Thymus Enzymatic Polypeptide Fractions[1]	183.33 mg
Thymus Extract	16.66 mg
Raw Spleen (spray/freeze dried)	43.33 mg
Raw Lymph (spray/freeze dried)	21.66 mg
Raw Bone Marrow (spray/freeze dried)	21.6 mg
Raw Pituitary (spray/freeze dried)	3.33 mg

Trypsin (1:75)	8.33 mg
Bromelain (1:1200 MCU)	16.66 mg
Papain (600)	6.66 mg
Enchinacea Angustifolia Extract	266.66 mg
Iris Versicolor Extract	43.33 mg
Hydrastis Canadensis Extract	28 mg
Vitamin A (Beta Carotene)	833.33 IU
Vitamin D (Colecalciferol)	66.67 IU
Vitamin C (Ascorbic acid, buffered and esterified)	83.33 mg
Vitamin E (d-Alpha tocopherol succinate)	10 IU
Vitamin B-1 (Thiamine Mononitrate)	4.17 mg
Vitamin B-2 (Riboflavin)	4.17 mg
Vitamin B-6 (Pyridoxine Hydrochloride)	4.17 mg
Vitamin B-12 (Cyanocobalamin)	8.33 mcg
Pantothenic Acid (Calcium Pantothenate)	8.33 mg
Niacinamide	8.33 mg
Biotin	50 mcg
Folic Acid	66.67 mcg
PABA (Para Amino Benzoic Acid)	4.17 mg
Choline (Bitartrate)	16.67 mg
Inositol	41.67 mg
Calcium (Carbonate)	25 mg
Iodine (Kelp)	25 mcg
Magnesium (Gluconate)	16.67 mg
Manganese (Gluconate)	.83 mg
Selenium (Chelate) (Gluconate)	8.33 mcg
Chromium (Picolinate)	8.33 mcg

Copper (Gluconate)	.33 mg
Potassium (Gluconate)	8.33 mg
Zinc (Gluconate)	2.5 mg
Boron	0.167 mg
Rutin	4.167 mg
Hesperidin	.83 mg
Citrus Bioflavonoid	4.16 mg
Betaine HCl	4.16 mg
Octacosanol	62.5 mcg
L-Lysine	4.167 mg
Amino Acid Complex[2]	4.167 mg

[1]Fractions and Extracts include Thymosin, Thymopoietin and Thymic Humoral Factor (THF)

[2]Amino acid complex contains the L form of the following amino acids: arginine, cysteine, histidine, ornithine, isoleucine, leucine, threonine, tyrosine, valine, phenylalanine, methionine.

The combination of the above elements is the first time these elements have been combined with the improved absorption and delivery system. The improved formulation produces a better dosing regimen and improved response in humans and animals. The novel compositions of the present invention have altered components that are different from other dietary supplements. The Vitamin C is esterified and buffered for less stomach complications. There is a greater amount of thymus extract than in other formulations. A novel formulation of glandular ingredients is found in the compositions of the present invention. Both the vitamin components and the glandular components have been hydrolyzed for increased solubility and improved absorption by the body. Other absorption improving steps include chelating the amino acids and minerals to increase bodily absorption and to reduce the elimination of the components. The

mineral boron provides improved absorption capability to the compositions of the present invention. Beta carotene can be added to the coating of a tablet to aid in swallowing and to mask the odor of the thymus and vitamin components. Digestive enzymes are another component of the compositions of the present invention.

The above composition may be formulated into any type of dosing system. The invention is not limited to a tablet or captab, but may also be dispensed in liquid or other forms known to those skilled in the art. Additionally, the compositions of the present invention may be introduced into the body in other ways, such as by injection, that are well known to those skilled in the art.

The compositions described above can be provided as pharmaceutically acceptable formulations using formulation methods known to those of ordinary skill in the art. These formulations can be administered by standard routes. In general, the combinations may be administered by the topical, transdermal, oral, rectal or parenteral (e.g., intravenous, subcutaneous or intramuscular) route. In addition, the compositions may be incorporated into biodegradable polymers allowing for sustained release of the compositions.

The dosage of the compositions may depend on the condition of the human being treated and other clinical factors such as weight and condition of the human and the route of administration of the composition. For oral administration to humans, the formulation described above in the doses described below, provides a sufficient supply of the elements of the composition to supplement the diet. Approximately 1-12 times the amounts shown above for the elements of the present invention can be taken by humans or animals to maintain health. A preferred dose for healthy humans and animals would be to take approximately 6 times the amounts shown above, for each element, at multiple times during the day. For humans and animals with impaired health or under other physiological stress, more frequent administrations of approximately 6-20 times the amounts shown above, for each element, may be necessary. Additionally, lesser

doses may provide adequate dietary supplementation for some humans or animals. For oral administration to humans, a dosage of between approximately 3-24 times the amounts shown above for each element, given between approximately 1-3 times a day; preferably between approximately 3-18 times the amounts shown above for each element, given 2-3 times a day; and most preferably between approximately 3-12 times the amounts shown above, given 2-3 times a day, is generally sufficient. For animals, the dosages are adjusted for the weight and activity of the animal and the animal's overall physical condition. Approximately 0.25-3.0 doses of the above formulation can be given to small animals such as cats to supplement their diet and provide factors and cofactors. Approximately 2-6 doses of the above formulation can be given to larger animals such as dogs.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the compositions of the present invention and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the above compositions with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the compositions of the present invention; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, etc.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a

suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered composition moistened with an inert liquid diluent. The tablets may be optionally coated or scored and may be formulated so as to provide a slow or controlled release of the compositions of the present invention therein.

Formulations suitable for topical administration in the mouth include lozenges comprising the compositions of the present invention in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the compositions of the present invention in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the compositions of the present invention to be administered in a suitable liquid carrier.

Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising the ingredient to be administered in a pharmaceutical acceptable carrier. A preferred topical delivery system is a transdermal patch containing the compositions of the present invention to be administered.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of 20 to 500 microns which is administered in the manner in which snuff is administered, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations, wherein the carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, include aqueous or oily solutions of the compositions of the present invention.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the compositions of the present invention such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials and may be stored in freeze-dried (lyophilized) conditions requiring only the addition of a sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the compositions of the present invention.

It should be understood that in addition to the compositions of the present invention, particularly mentioned above, the formulations of the present invention may include other agents conventional in the art, having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents.

This invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications and equivalents thereof which, after reading the description

herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the appended claims.

Example 1

The following formulation is made into a tablet delivery vehicle, such that two tablets provide six times the amounts shown below for each element. The measurements shown provide the relative amounts of each element. The elements include:

Vitamin E (d-alpha tocopherol succinate)	66.6 IU
Vitamin C (Ascorbic Acid, buffered and esterified)	83.33 mg
Vitamin B-1 (Thiamine Mononitrate)	10 mg
Copper (Proteinate)	100 mcg
Zinc (Proteinate)	5 mg
Selenium (Proteinate)	18.33mcg
L-Lysine	83.33 mg
Thymus Enzymatic Polypeptide Fractions	183.33 mg
Thymus Extract	16.66 mg
Fractions and Extracts include Thymosin, Thymopoietin, and Thymic Humoral Factor (THF)	
Raw Spleen (spray/freeze dried)	43.33 mg
Raw Lymph (spray/freeze dried)	21.66 mg
Raw Bone Marrow (spray/freeze dried)	21.66 mg
Raw Pituitary (spray/freeze dried)	3.33 mg
Trypsin (1:75)	8.33 mg
Bromelain (1:1200 MCU)	16.66 mg

Papain (600)	6.66 mg
Enchinacea Angustifolia Extract	266.66 mg
Iris Versicolor Extract	43.33 mg
Hydrastis Canadensis Extract	28 mg
Vitamin A (Beta Carotene)	833.33 IU
Vitamin D (Colecalciferol)	66.67 IU
Vitamin C (Ascorbic acid, buffered and esterified)	83.33 mg
Vitamin E (d-Alpha tocopherol succinate)	10 IU
Vitamin B-1 (Thiamine Mononitrate)	4.17 mg
Vitamin B-2 (Riboflavin)	4.17 mg
Vitamin B-6 (Pyridoxine Hydrochloride)	4.17 mg
Vitamin B-12 (Cyanocobalamin)	8.33 mcg
Pantothenic Acid (Calcium Pantothenate)	8.33 mg
Niacinamide	8.33 mg
Biotin	50 mcg
Folic Acid	66.67 mcg
PABA (Para Amino Benzoic Acid)	4.17 mg
Choline (Bitartrate)	16.67 mg
Inositol	41.67 mg
Calcium (Carbonate)	25 mg
Iodine (Kelp)	25 mcg
Magnesium (Gluconate)	16.67 mg
Manganese (Gluconate)	.83 mg
Selenium (Chelate) (Gluconate)	8.33 mcg
Chromium (Picolinate)	8.33 mcg
Copper (Gluconate)	.33 mg

Potassium (Gluconate)	8.33 mg
Zinc (Gluconate)	2.5 mg
Boron	0.167 mg
Rutin	4.167 mg
Hesperidin	.83 mg
Citrus Bioflavonoid	4.16 mg
Betaine HCl	4.16 mg
Octacosanol	62.5 mcg
L-Lysine	4.167 mg
Amino Acid Complex	4.167 mg

The amino acid complex includes the L forms of the following amino acids: arginine, cysteine, histidine, ornithine, isoleucine, leucine, threonine, tyrosine, valine, phenylalanine and methionine. The thymus enzymatic polypeptide fractions include the following thymic factors: thymosin, thymopoietin, thymic humoral factor (THF). The product is prepared in a natural based composition of alfalfa leaf extract, deoxyribonucleic acid, brewer's yeast, wheat germ extract, ribonucleic acid, watercress, lecithin extract, glutamic acid, apple pectin, yogurt culture and acidophilus, kelp and bone meal. A natural protective coating is provided on the captab.

The tablet is administered to the patient two times a day. The patient takes the tablets with food and has eight glasses of water each day.

The patient supplements her diet with the above composition. The patient has been diagnosed with systemic lupus erythematosis (SLE). After taking the above composition, the blood of the patient is tested and an increase in Thymosin-Alpha 1 levels is found in the patient's serum. After continued supplementation of her diet with the above composition, the patient becomes SLE asymptomatic.

Example 2

The composition in the dosage amounts of Example 1 is used to supplement the diet of a patient chronically infected with Hepatitis B virus. After continued dietary supplementation, the patient no longer tests positive for active Hepatitis B virus infection.

Example 3

The composition in the dosage amounts of Example 1 is used to supplement the diet of a patient with rheumatoid arthritis. After continued dietary supplementation, the patient no longer has arthritic symptoms.

Example 4

The composition in the dosage amounts of Example 1 is used to supplement the diet of a patient chronically infected with Hepatitis C virus. After continued dietary supplementation, the patient no longer tests positive for active Hepatitis C virus infection.

It should be understood, of course, that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and the scope of the invention as set forth in the appended claims.

What is claimed is:

1. A composition comprising thymic-derived factors and enzymatic co-factors.

2. The composition of claim 1, wherein the thymic-derived factors are selected from the group consisting of thymus extract, thymus enzymatic polypeptide factors, thymosin, thymopoietin and thymic humoral factor.

3. The composition of claim 1, wherein the enzymatic co-factors are selected from the group consisting of vitamins and minerals.

4. The composition of claim 3, wherein the vitamins are selected from the group consisting of vitamins A, D, C, E, B-1, B-2, B-6 and B-12.

5. The composition of claim of any of claims 1-4, further comprising glandular factors.

6. The composition of claim 5, wherein the glandular factors are selected from the group consisting of raw spleen, raw lymph, raw bone marrow and raw pituitary.

7. The composition of claim 6, wherein the glandular factors are bovine.

8. The composition of any of claims 1-7, further comprising amino acids.

9. The composition of claim 8, wherein the amino acids are selected from the group consisting of arginine, cysteine, histidine, ornithine, isoleucine, leucine, threonine, tyrosine, valine, phenylalanine and methionine.

10. A composition consisting essentially of thymus enzymatic polypeptide fractions, thymus extract, raw spleen, raw lymph, raw bone marrow, raw pituitary, vitamins A, D, C, E, B-1, B-2, B-6 and B-12, folic acid, niacinamide, biotin, pantothenic acid, calcium, iodine, magnesium, copper, zinc, selenium, potassium, manganese, chromium, boron, hesperidin, inositol, citrus bioflavinoid, choline, betaine HCl, octacosanol, para amino benzoic acid, rutin, trypsin, bromelain, papain, Echinacea angustifolia extract, Iris versicolor extract, Hydrastis canadensis extract, L-lysine, L-arginine, L-cysteine, L-histidine, L-ornithine, L-isoleucine, L-leucine, L-threonine, L-valine, L-phenylalanine and L-methionine.

11. The composition of claim 10, wherein the thymus enzymatic polypeptide factors are selected from the group consisting of thymosin, thymopoietin and thymic humoral factor.

12. A method of increasing serum levels of thymosin alpha 1 in a subject comprising administering to the subject the composition of any of claims 1-11.

13. A method of enhancing the immune system of a subject by increasing serum levels of thymosin alpha 1 in the subject comprising administering to the subject the composition of claims 1-11.

14. A method of treating an autoimmune disease in a subject by increasing serum levels of thymosin alpha 1 in the subject comprising administering to the subject the composition of claims 1-11.

15. A method of treating an autoimmune disease in a subject, comprising administering to the subject the composition of claims 1-11.

16. The method of claims 14 or 15, wherein the autoimmune disease is selected from the group consisting of systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis.

17. A method of treating a viral infection in a subject comprising administering to the subject the composition of any of claims 1-11.

18. The method of claim 17, wherein the viral infection is caused by a virus selected from the group consisting of Hepatitis A virus, hepatitis B virus, hepatitis C virus, herpes virus and human immunodeficiency virus.

19. A method of enhancing athletic performance in a subject by increasing hematocrit and reducing recovery time in the subject comprising administering to the subject the composition of any of claims 1-11.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19564

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 47/00
US CL : 424/439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/439

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS
thymic, thymus, thymopoietin, thymosin, vitamins, minerals, amino acids, immune, lupus, arthritis, virus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,698,221 (STRAUB) 06 October 1987, column 1, lines 12-63; claims 1-20.	1-4
Y	US 4,826,680 A (JAEGER) 02 May 1989, column 1, lines 41-49; column 2, lines 21-36; claims 1-17.	1, 8, 9, 10-18
Y	US 4,863,898 A (ASHMEAD et al) 05 September 1989, see entire document.	5-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
07 JANUARY 1998

Date of mailing of the international search report
10 FEB 1998

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